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Scopolamine-Induced Impairment in Concurrent Fixed-Interval Responding in a Radial Maze Task

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SESSIONS, G. R., J. J. PILCHER AND T. F. ELSMORE. *Scopolamine-induced impairment in a concurrent fixed-interval radial maze task*. PHARMACOL BIOCHEM BEHAV **59**(3) 641–647, 1998.—The present study investigated the effects of scopolamine hydrobromide (SCOP; 0.06–1.0 mg/kg IP) and its quartenary analogue, scopolamine methylbromide (SCOPMB), on performance in a radial arm maze foraging task, to dissociate general drug-induced alterations of motor performance from measurement of impairments on more complex behaviors involving timing and memory. In this paradigm, rats are trained to free run a radial maze under an eight-alternative concurrent fixed-interval (FI) schedule of food reinforcement. The eight FIs (55 to 759 s) were assigned randomly to the arms of the maze, with a different pattern for each animal. SCOP produced dose-dependent degradation in response patterning and response rates in the concurrent FI schedules without significantly affecting the rates of arm entries or arm traversal latencies. The peripheral cholinergic antagonist, SCOPMB, generally produced small to moderate depressions in all measures with the exception of patterning of arm entries and pellets earned, but there were no clear dose–response relationships evident in the data. These results are consistent with the notion that central cholinergic mechanisms are involved in the mediation of complex conditioned behaviors. © 1998 Elsevier Science Inc.

Scopolamine Anticholinergic drugs Fixed-interval responding Memory Radial maze Foraging task Rat

CENTRAL cholinergic systems frequently have been implicated as involved in the mediation of learning and memory processes, both in humans (5,6,9,10,32) and in nonhuman animals (3,4,8,14,23,31,37). Corroborating evidence comes from studies utilizing multiple techniques and approaches, including lesion studies (13,22,26,28,29,33), direct subdural chemical stimulation (27), and various pharmacological manipulations (1,2,7,16,18). Evidence from numerous drug studies support the notion that blockade of cholinergic muscarinic receptors with agents such as scopolamine interfere with acquisition of new tasks and performance of a variety of previously learned responses (1,18). Additionally, cholinergic agonists, such as physostigmine, have been shown to produce improvements in learning and memory paradigms (1,7,17,27).

Such evidence, however, has not been accepted unequivocally. Specifically, studies using scopolamine have been criticized due to the overall debilitating effects of the drug on performance in general (12,24,25,30,38). It has proven difficult to separate the effects of scopolamine upon general motoric functioning from specific effects on learning, memory, or the performance of complex conditioned responses.

The general objective of the present study was to measure the effects of central muscarinic receptor blockade with scopolamine hydrobromide upon both general motoric functioning and performance of a complex conditioned behavior involving response timing and memory. A novel radial arm maze "foraging" task has recently been developed (13), and for the first time was used in the present study to characterize drug effects on performance of a complex conditioned task. This paradigm offers the advantages of combining the spatial learning and memory aspects of the radial maze model with standardized operant models that have long been in use in psychopharmacological laboratories. In this paradigm, rats are trained to run in an eight-arm radial maze and to perform

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a nose-poke task for food under an eight-alternative concurrent fixed-interval schedule of reinforcement. This task provides the opportunity to study drug-induced changes in a variety of stabilized behaviors associated with performance of the task. Measures are obtained that are influenced heavily by motoric functioning, such as rates of arm entries and rates of nose-poke responses for food. In addition, measures may be obtained that are sensitive to changes in response timing independent of overall rates of behavior, such as measures reflecting the average distribution of responses across the fixed intervals in effect in the schedule.

The present study used this task as an assay for documenting and analyzing the effects of scopolamine on a variety of measures associated with the foraging paradigm. Specific issues addressed were 1) comparisons of dose–effect functions on measures of motoric behaviors and measures of response timing on the concurrent fixed-interval task, and 2) the contribution of central vs. peripheral cholinergic blockade to the performance degrading effects of scopolamine. The latter issue was addressed in an experiment in which a methylate form of scopolamine not thought to cross the blood–brain barrier (15), scopolamine methylbromide, was substituted for scopolamine hydrobromide in the same behavioral paradigm.

METHOD

Subjects

Six male Sprague–Dawley rats (Zivic Miller Laboratories, Allison Park, PA), approximately 90 days old at the beginning of the experiment, served as subjects. The animals were housed individually in acrylic rack-mounted cages with pine sawdust bedding in an air-conditioned colony room. The room was maintained under a 12 L:12 D cycle (light onset at 0600 h). After arrival in the laboratory, the animals were allowed ad lib access to food (Purina Rat Chow) and water until they reached free-feeding weights of 360–390 g. Food was then restricted gradually over the next 2 weeks until body weights were reduced to 90% of free-feeding body weights. Thereafter, the animals were maintained at approximately this weight through restricted postsession feeding of food chow in addition to food received in the maze. All animals were drug naive prior to the present experiment.

Apparatus

The experiment was conducted in a totally enclosed eight-arm radial maze, illustrated in Fig. 1. Each arm of the maze was 19.7 cm wide and 61 cm in length, with walls extending 12.7 cm in height. The arms extended from an octagonal center compartment that was 51.5 cm in diameter and the same height as the arms. Removable lids permitted experimenter access to the arms and center compartment. The maze was constructed from 6.25 mm polycarbonate plastic, and all parts except the floor and the end walls were transparent. The floor was black and the end walls were constructed from commercial laboratory rat test modules and blank aluminum inserts (Coulbourn Instruments, Allentown, PA). The maze was elevated 75 cm from the floor on stainless steel legs. Each arm was equipped with a photocell sensor 15 cm from its entrance and a photocell-equipped recessed food trough (Coulbourn Instruments) located in the end wall. A 1.27 cm miniature stimulus light with clear jeweled cover was mounted in the end wall 10.16 cm above the floor and 5.08 cm from the right wall. A dispenser (Coulbourn Instruments) for delivering 45 mg food pellets (Dustless Purified Diet Precision Pellets, Bio-Serv, Frenchtown, PA) into the food trough was mounted behind the end wall as was a relay module, which produced an audible click when the food trough photocell was interrupted. The entrance to the arms could be blocked by vertical guillotine gates manually operated from a distance via strings suspended from the ceiling and traversing to the experimenter station approximately 3 meters away. The maze was housed in an air-conditioned room and surrounded on all sides by walls, equipment racks, or office separator panels made visually discriminable by the addition of 24-cm high symbols consisting of a plus sign or triangle. A laboratory computer (PDP 11/73, Digital Equipment Corporation, Nashau, NH) running SKED-11 software [(34); State Systems, Inc., Kalamazoo, MI] was interfaced with each device in the maze via Lablink interface modules (Coulbourn Instruments) and was used to detect arm entries and exits, nose pokes into the food troughs, and to program delivery of food pellets.

Procedures

Shaping. The animals were handled briefly each day for the week prior to the beginning of the experiment. Additionally, they were fed the reinforcement food pellets as part of their food ration on the day prior to shaping, and were then food deprived for 24 h. After a week of adaptation to handling, each animal experienced 1 day of general exposure to retrieving pellets in the arms of the radial maze. Each animal was placed into an arm of the maze that had been reduced to approximately 23 cm in length via the addition of a temporary cardboard wall opposite the food trough. The food trough was baited with a food pellet. When the animal investigated the food trough and ate the food pellet, the nose poke interrupted the photocell and another pellet was delivered. The animals were thus allowed to nose poke for food on a continuous reinforcement schedule (CRF) until 20 food pellets had been obtained and eaten in the first arm. They were then removed and placed in an adjacent arm similarly modified in length and allowed to nose poke for 20 additional pellets on the CRF

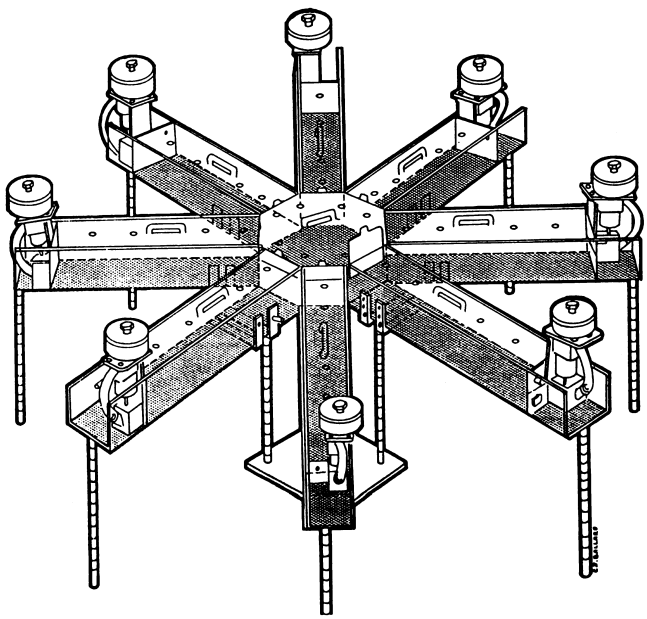

FIG. 1. Schematic of the eight arm radial maze. Not to scale.

schedule. They were then removed to a third modified arm and allowed to obtain another 20 pellets, but the schedule was changed such that a pellet was delivered for every fourth nose poke (fixed Ratio 4 or FR4 schedule). This procedure was repeated in a fourth arm. The animals were then introduced into the end of another arm with no barrier modification and allowed to traverse the arm and nose poke for another 20 pellets on a FR4 schedule. This procedure was repeated in one more arm to conclude the initial shaping, magazine training, and maze familiarization stage of training.

Baseline training. On the following day, the animals entered the training phase of the study, designed to produce stable baseline responding on the task prior to drug administrations. The animals received daily 1-h training sessions in the maze until responding stabilized on all measures (approximately 50 sessions) as indicated by visual inspection of cumulative records of rate of arm entries and nose-poke responses. The test sessions for training and drug administration phases of the study were identical with the exception of administration of drugs or vehicle. To begin a test session, the animals were placed in the center compartment of the maze with the guillotine doors blocking access to the arms. Approximately 10 s later the stimulus lights were illuminated at the end of the arms, the doors were raised, and the animals were allowed free access to all parts of the maze for 1 h. Nose pokes into the food troughs were reinforced according to different fixed-interval (FI) schedules of reinforcement associated with each arm. The animals received a food pellet upon the first nose poke into the food trough of a particular arm following the expiration of a specified time interval determined by the FI value associated with each arm (an eight-alternative concurrent FI schedule of reinforcement). The FI values (55, 92, 129, 203, 314, 425, 574, and 759 s) were assigned randomly to the arms of the maze, with a different pattern for each animal. The FI values were multiples of a list of prime numbers selected so that delivery of food in one arm would not predict food availability in another. For each animal, the assignment of FI values to individual arms was always the same. Time–event data were collected for each arm entry, nose poke, and pellet delivery and were stored for subsequent analysis.

Drug test sessions. Drug tests consisted of administering drug or vehicle injections to the animals immediately prior to placing them into the maze. Otherwise, the procedures were identical to baseline training sessions. Drug or vehicle was administered on Tuesdays and Fridays, and baseline test sessions were conducted on the remaining 3 days of the week. Scopolamine hydrobromide, scopolamine methylbromide (Sigma Chemical Co., 0.06, 0.12, 0.25, 0.5, and 1.0 mg/kg) or vehicle (0.9% NaCl) was injected IP in volumes of 0.1 cc/100 g body weight immediately prior to test sessions. Drug or vehicle sessions were separated by at least 72 h and were always preceded by a control session in which no injections were made. Testing was conducted first with scopolamine hydrobromide (SCOP), then with scopolamine methylbromide (SCOPMB). Between these drug series, which were separated by several months, the animals were exposed to other drugs, including the benzodiazepine-related compounds diazepam, triazolam, and zolpidem, and they were continuously run in the maze according to the schedule detailed above. During each drug series, drugs were administered in a counterbalanced, nonsystematic order. To provide a means to stabilize the variability in the data, the procedures for the first drug series were repeated for each drug. Test sessions were conducted for individual subjects at approximately the same time each day between 0900 and 1600 h.

Behavioral measures. The following measures were obtained for each test session. Entries—the number of entries into each arm, defined as a beam break of the entry photocell. Nose-poke responses—the total number of nose pokes emitted in each arm. Pellets—the total number of pellets obtained in each arm. Arm traversal latency—the average latency in seconds between arm entry and nose poke for each arm, obtained by dividing the cumulative latencies by the number of arm entries. Response rate—the total number of responses emitted in an arm divided by the accumulated time in seconds spent in that arm during the test period. Responses per entry—this measure was derived by dividing the total number of responses by the total entries for each arm. Time per entry—the total time in seconds spent in each arm divided by the total number of entries. Quarter life for responses—the quarter life (QL) measure represents the relative point in any given FI at which 25% of the total responses for that interval have been emitted. A QL of 25 results if responses are emitted either randomly or at a fixed rate. High QL measures under FI schedules of reinforcement indicate good temporal stimulus control with subjects emitting higher rates of responding relatively late in the interval. QL for responses represents the average quarter life for nose-poke responses for each interval for each arm. Quarter life for entries—the average QL for individual arm entries for each interval for each arm.

Statistical Analyses

The data were analyzed using SAS statistical software (SAS Institute, Inc., Cary, NC) within a single-factor repeated measures analysis of variance (ANOVA) (21), with drug dose as the repeated factor. The data for individual arms of the maze were averaged prior to the ANOVA analyses. Behavior in the eight individual arms was examined by visual analysis of cumulative records and summary graphs. The data from the first and second drug series were averaged prior to the analyses, as replication of the drug series was designed primarily to reduce variability in the data. Examination of the source of significant main effects associated with SCOP dose was accomplished via post hoc individual comparisons of levels of drug dose using Tukey's Studentized Range Statistic (39). Alpha level for all tests of significance was set at 0.05.

RESULTS

Visual examinations of the individual cumulative records of rates of arm entries and nose-poke responses [see (13)] showed that SCOP had no systematic effects on arm entries, but overall nose-poke responses were decreased, beginning at the lowest dose 0.0625 mg/kg. The drug effects were apparent within 10 min, maximum effects were observable approximately 30 min following drug injection, and continued for the remainder of the hour-long test sessions.

The results of the ANOVA of the data for the 1-h test sessions for individual measures revealed significant effects for drug dose for the measures nose pokes, response rates, responses per entry, QL for responses, QL for entries, and pellets, $F(5, 25) = 8.79$, 6.36, 8.53, 9.48, 9.03, and 4.21, respectively, $p < 0.05$).

Grouped data for arm entry and nose-poke responses, response rates and traversal latencies are shown in Fig. 2. The panels on the left of Fig. 2 for each measure represent the group averages of each measure by FI length and drug dose. The panels on the right represent the totals (arm entries, nose-poke responses, pellets), or averages (response rate, arm traversal latency, responses per entry, QL for entries, and QL

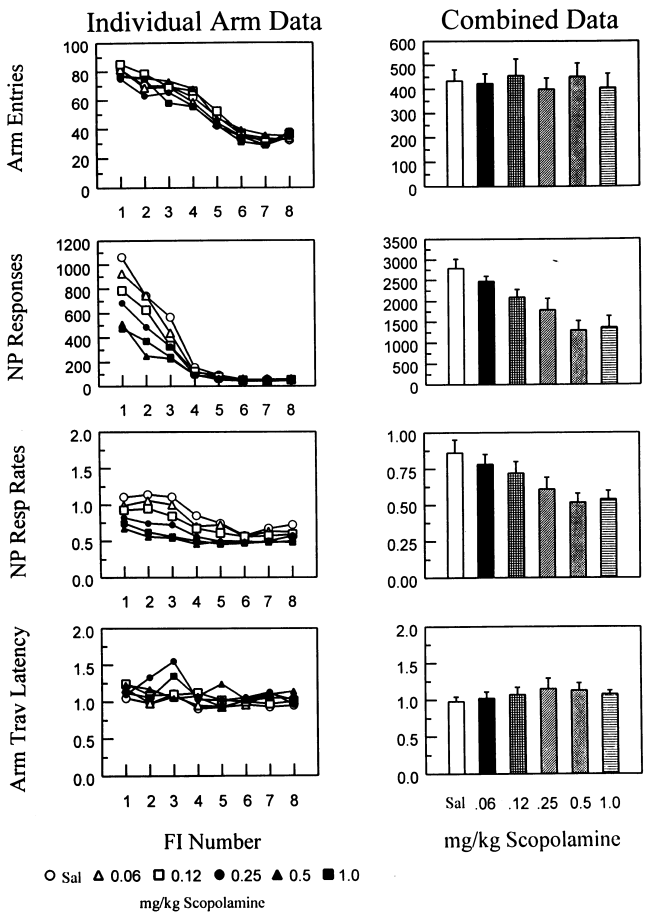

FIG. 2. Left panels, top to bottom: mean arm entries, nose-poke responses, nose-poke response rates (per second), and arm traversal latencies (in seconds) by fixed interval (FI) numbers 1–8 for vehicle and SCOP test sessions. FI durations: 1 = 55 s, 2 = 92 s, 3 = 129 s, 4 = 203 s, 5 = 314 s, 6 = 425 s, 7 = 574 s, 8 = 759 s. Individual data points represent average of two replications. Right panels: mean (±SEM) of same measures, by drug dose in mg/kg, combined across all arms for vehicle and SCOP test sessions.

for responses) for each measure for 1-h test sessions collapsed across the eight FI intervals (eight arms of the maze).

As can be seen in the saline control data plotted in the left panels of Fig. 2, under vehicle conditions the animals generally distributed their arm entries and nose-poke responses inversely according to the length of the FIs in effect in the arms. Arm entries decreased in a roughly linear manner from the shortest to longest FI value. Similarly, nose-poke responses were systematically related to FI values from 55 to 203 s, but decreased dramatically at the longer FI values.

The right panels of Fig. 2 illustrate the data collapsed, or totaled, across all eight arms. These grouped data reveal no significant effects of SCOP on arm entries. However, Fig. 2 illustrates that nose-poke responses were decreased by SCOP in a dose-dependent manner, with doses of 0.25 mg/kg and above producing significantly fewer total nose pokes compared with vehicle. The magnitude of these effects varied directly with FI value, with maximal effects on nose pokes in the arm programmed with the shortest FI.

The effects of SCOP on nose-poke response rates are also shown in Fig. 2. The average nose-poke rate in the arms with the three shortest FI lengths was slightly higher than one per second, and decreased to approximately one response every 1.33 s in the other five arms (left panel). SCOP decreased response rates in a dose-dependent manner, with average rates over all arms significantly depressed at doses of 0.25 mg/kg and above (right panel).

Figure 2 also shows the average arm traversal latency measures, reflecting the speed of running. SCOP produced no significant effects on arm traversal times, indicating no drug-induced changes in speed of running the maze.

Figure 3 illustrates the data for the measures responses per entry, QL for entries, QL for responses, and pellets. SCOP produced dose-dependent decrements in the average number of nose-poke responses per arm entry, as can be seen in the left panel of Fig. 3. This measure correlates very closely with total responses, because SCOP did not significantly affect the

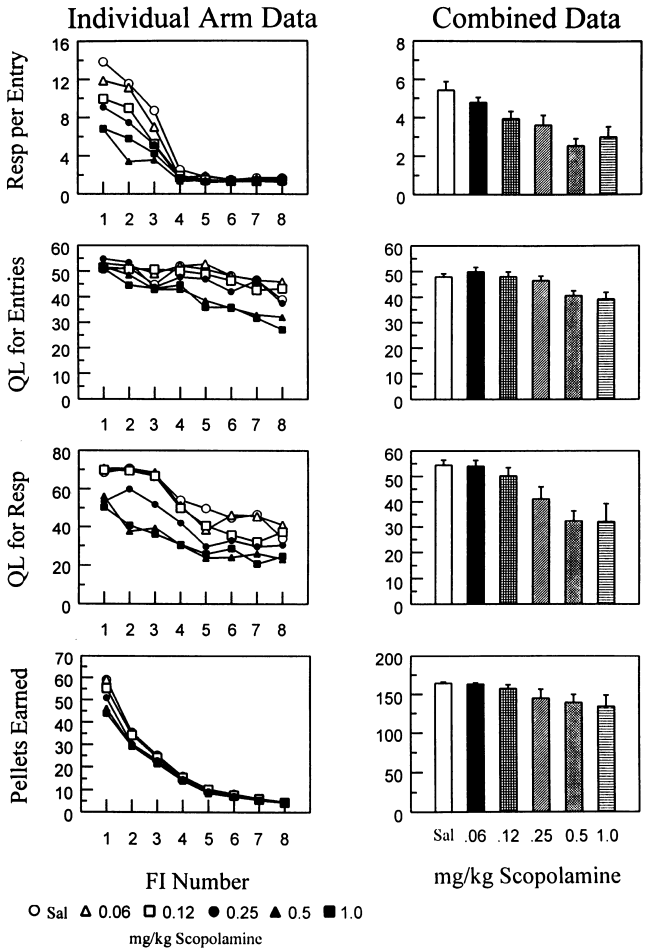

FIG. 3. Left panels, top to bottom: mean responses per entry, QL for entries, QL for responses, and pellets earned by FI numbers 1–8 for vehicle and SCOP test sessions. FI durations: 1 = 55 s, 2 = 92 s, 3 = 129 s, 4 = 203 s, 5 = 314 s, 6 = 425 s, 7 = 574 s, 8 = 759 s. Individual data points represent average of two replications. Right panels: mean (±SEM) of same measures, by drug dose in mg/kg, combined across all arms for vehicle and SCOP test sessions.

number of arm entries. The average number of responses per entry decreased from approximately 14 to 9 in the three richest arms, then dropped sharply to less than three for the remaining five arms. As can be seen in the right panel of Fig. 3, SCOP produced significant decrements in total average responses per entry at doses of 0.125 mg/kg and above.

The quarter life values associated with FI response patterns for arm entries and nose-poke responses are also illustrated in Fig. 3. Under control conditions the QL for entries were comparable across FI values (left panel). SCOP produced a small dose-dependent depression in this measure, with significant depression observable at doses of 0.50 mg/kg and higher, compared with control measures.

The QL for responses measure for nose pokes under control conditions was uniform and high for FI values from 55–129 s, then decreased substantially for FI values of 203 s and greater (left panel). At these longer FI values, however, QL for responses still averaged approximately 50%, indicating some temporal control of nose-poke responding. In other words, in the arms with longer FI lengths, the rats on the average emitted approximately 75% of their responses in the last 50% of the interval. SCOP produced a dose-dependent decrease in QL for responses, which was most evident in the arms with the higher baseline QL measures (right panel). SCOP doses of 0.50 mg/kg and above significantly decreased QL for responses compared with vehicle. Based on the dichotomous grouping of baseline QL for responses values for the arms programmed with the shorter FI lengths from 55 to 129 s (where QL for responses averaged approximately 70%) vs. arms with FI lengths from 203 to 759 s (where QL for responses values averaged approximately 50%), the data from the three arms with the shortest FI lengths were analyzed separately. This analysis revealed results similar to those previously discussed.

Under control conditions, the number of pellets obtained by the rats in each arm varied inversely with the length of the FI, as can be seen in the left panel of Fig. 3. SCOP produced a dose-dependent depression in the total number of pellets obtained only at the highest dose, 1.0 mg/kg, compared with the vehicle (right panel). The magnitude of the effect was greatest at the shortest FI lengths.

In contrast to the dose-dependent effects of SCOP on affected measures of performance, SCOPMB generally produced small to moderate nonlinear depressions of behavior on most variables, with statistically significant effects associated with only the highest dose level, 1.0 mg/kg. ANOVA revealed significant effects for drug dose for nose-poke responses, arm entries, response rates, responses per entry, QL for responses, and pellets, $F(5, 25) = 4.74, 7.02, 4.78, 3.12, 3.97$, and 2.61, respectively, $p < 0.05$. Figure 4 illustrates the effects of SCOPMB on nose-poke responses, as representative of the drug's effects on motoric behaviors, and on QL for responses as representative of effects on complex conditioned behaviors. On both measures, SCOPMB produced general depressions of behavior that were nonlinear and statistically significant only at the highest dose, 1.0 mg/kg. This was the typical pattern of observed results.

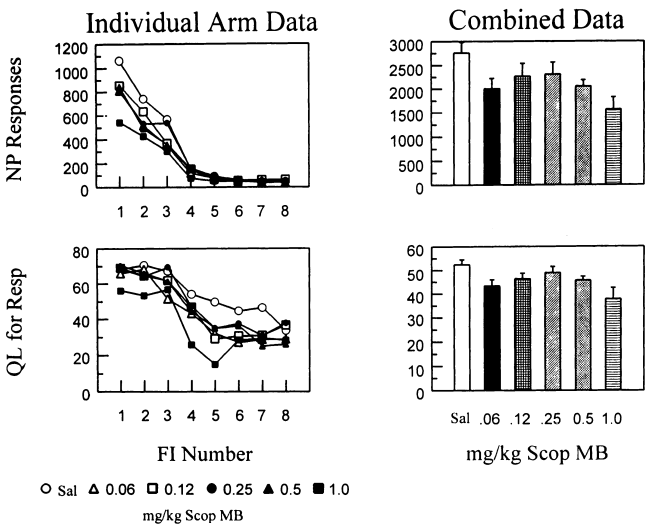

FIG. 4. Left panels, top to bottom: mean nose-poke responses and QL for responses by FI numbers 1–8 for vehicle and SCOPMB test sessions. FI durations: 1 = 55 s, 2 = 92 s, 3 = 129 s, 4 = 203 s, 5 = 314 s, 6 = 425 s, 7 = 574 s, 8 = 759 s. Individual data points represent average of two replications. Right panels: mean (±SEM) of same measures, by drug dose in mg/kg, combined across all arms for vehicle and SCOPMB test sessions.

DISCUSSION

Scopolamine produced dose-dependent degradation in response timing required for temporal discriminations in the concurrent FI schedules and in response rates without significantly affecting the primary measures of motoric behaviors, arm entries, and arm traversal latencies. At doses of 0.25 mg/kg and above, the drug produced significant depressions in nose-poke response rates and the average number of nose-poke responses per arm entry, and at 0.50 mg/kg and above, depressions in QL for responses.

These effects are more likely attributable to the central, rather than peripheral, effects of scopolamine, as the pattern of effects produced by the peripheral acting antimuscarinic, scopolamine methylbromide, was qualitatively different and not related to dose in a linear manner. SCOPMB produced small to moderate depressions in all measures, with the exception of QL for entries and pellets earned, but these effects were observable trends in the data at the lowest dose used as well as the highest dose, and there were no clear dose–response relationships evident in the data. Additionally, these effects were less in magnitude, overall, than those produced by SCOP, in that the perturbations in behavior did not result in a significant depression of the total number of pellets earned during the sessions. These behavioral effects of peripheral cholinergic blockade by SCOPMB may be interpreted either as an indication of generalized performance impairment in motoric behaviors as a result of drug-induced malaise, or, in the case of the high dose effects, possible central stimulation due to leakage of the blood–brain barrier to the methylated scopolamine. Peripheral cholinergic blockade has been shown to impair behavior in a number of tasks involving motoric components, and the results of the present study are consistent with those studies (11,19,20,35,36). The generalized depression of behavior at low doses and the absence of clear dose–effect functions, contrasting with the effects of SCOP, would appear to favor peripheral, rather than central, mechanisms of action of SCOPMB in producing the observed pattern of effects in the foraging task in the radial maze.

Scopolamine significantly impaired temporal discrimination, as indicated by decrements in QL for both entries and nose-poke responses at doses of 0.50 mg/kg and larger. De-

creases in quarter life measures in FI responding are usually interpreted as indicating earlier responding within intervals, or a "flattening" of the usual FI curve of responding across time. The depression of QL for responses was most evident for the three shortest FI values, where response rates were the highest. SCOP-induced disruption in the temporal patterning of responses suggests a loss of stimulus control under the FI schedules in effect, and may reflect a loss of working memory for time since last reinforcement.

The drug-induced reduction in response rates and total response output at SCOP doses higher than 0.25 mg/kg might at first appear to have the overall result of increasing the efficiency of responding on the FI schedules, because total pellets earned were not significantly decreased except at the highest drug dose, 1.0 mg/kg. Even at this dose, the overall ratio of average responses to average pellets earned was lower than under control conditions. Reductions in response to reinforcement ratios are generally considered to reflect greater efficiency of responding on FI schedules, because reinforcement delivery is strictly timed and unrelated to response output, as long as some minimal rate of responding is maintained.

However, if the same analysis is made using the measure of ratio of arm entries to pellets earned, a substantial argument can be made that SCOP decreased, rather than increased, the efficiency of responding. In the radial maze foraging paradigm considerably more physical effort and energy is expended by the animals in traversing from one arm to another than is expended in executing nose-poke responses at the food dispenser. The data showed that SCOP produced a gradual reduction in pellets earned across increasing drug doses, and a significant reduction at 1.0 mg/kg. Thus, the ratio of average arm entries to average reinforcements earned was gradually reduced across drug doses, reflecting more energy expenditure per pellet earned than under control conditions. This would reflect a predictable consequence of the impairment in temporal discrimination that was indicated by the decrements in QL for both entries and responses at doses of 0.50 and 1.0 mg/kg. As stimulus control was diminished by SCOP, the relative efficiency of response timing for entries into the various arms associated with the multiple concurrent FI schedules was reduced, thereby resulting in increased entries per reinforcement delivery. Although measures were not made of the delay in time between reinforcement setup and actual delivery, it is arguable that this measure may have also increased, as would be expected if overall timing of entries and nose-poke responses was decremented.

The present experiment revealed strong effects of scopolamine on performance of a complex conditioned behavior, that of responding on the concurrent fixed-interval schedule of reinforcement. No evidence was obtained that the performance-degrading effects of the drug were related to general motoric slowing, general performance impairments, or peripheral as opposed to central cholinergic blockade. Quite the opposite, the effects of scopolamine were limited to those aspects of the task requiring accurate timing of the operant response most conditioned under the temporal schedules in effect in the various arms. The overall impact of alterations in response timing reinforcement density was a gradual reduction in number of pellets earned over the 1-h session, with significant reductions observed at only the highest dose.

These results are consistent with the notion that cholinergic mechanisms are involved in the mediation of complex conditioned behaviors. Furthermore, the use of the radial arm maze foraging task permitted the documentation and dissociation of the central and peripheral effects of scopolamine on general motoric performance from its effects on conditioned behaviors, clearly supporting previous studies that implicate cholinergic blockade in the disruption of complex conditioned behaviors.

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